J. PROTOZOOL. **24**(3), 475-478 (1977).

Essay and Reviews of Recent Symposia on Protozoan Chemotherapy

SEYMOUR H. HUTNER
Haskins Laboratories at Pace University, 41 Park Row, New York, New York 10038

WHAT follows is a series of reviews of recent symposia on antiprotozoal chemotherapy, with a review of the reviews at the end.

Elliott, K., O'Connor, M., Wolstenholme, G. E. W., eds. 1974. *Trypanosomiasis and Leishmaniasis with Special Reference to Chagas' Disease.* Ciba Foundation Symposium 20 (n. ser.). Associated Scientific Publishers, Amsterdam; American Elsevier, New York, 353 pp.; subject and author indices. $19.25.

Here is the concentrated sense of a 1973 Caracas gathering sponsored by Ciba-Geigy, the Venezuelan Academy of Sciences, and "La Trinidad" Medical Center of Caracas. The dust-jacket sets the main theme: a triatomid imposed on Latin America alongside a tsetse fly on Africa. Judged from the printed discussions, protozoologists from the U.S., Britain, and WHO struck sparks from their opposite numbers from afflicted areas. Contents: *Introduction.*—B. A. Newton beseeched eschewing of specialist jargon lest workers from diverse fields be confused. He was obeyed (or was the editing uncommonly sharp?). *Leishmaniasis and trypanosomiasis: the causative organisms compared and contrasted* (W. H. R. Lumsden).—Taxonomy of *Leishmania*; meditations on phylogeny of Trypanosomatidae; discussion includes counsels on cloning. *Epidemiology of African sleeping sickness* (J. R. Baker).—Tsetses and geography; the afterdiscussion has notes on new outbreaks and old endemic areas. *Epidemiology, modes of transmission and reservoir hosts of Chagas' disease* (R. Zeledón).—Includes review of infection from blood banks and placenta; discussion afterwards contains new information from E. Pifano on vector habitats and reservoir hosts; several discussants extol crystal violet to kill *T. cruzi* in blood banks (see below); Lumsden contends that the infectivity of *T. cruzi* (and even *T. brucei*) by nasal instillation, and probably by aerosols, dictates extreme care in handling; even laminar-flow cabinets are suspect. *Epidemiology of leishmaniasis; some reflections on causation* (R. S. Bray).—Engrossing field study in the Ethiopian highlands indicating cliff-dwelling *Hyrax* as host reservoir for cutaneous leishmaniasis, Bray as incidental host. *The African scene: mechanisms of pathogenesis in trypanosomiasis* (L. G. Goodwin).—"Trypanosomiasis has much the same hold on the African continent today as it had at the beginning of the century . . . the only really novel part of the picture is the appearance of the luxury hotels that have sprung up like mushrooms to cope with the flood of international tourists to the game reserves. Many have been built in the heart of the tsetse bush and some of them are dangerous places to work in or to visit. Human trypanosomiasis has been added to the list of African exports . . . New medicines for the treatment of human trypanosomes are scarce . . . the pharmaceutic industry does not find the difficult search for new drugs for a disease that affects a limited number of impoverished Africans an attractive financial proposition . . . new methods, different from the usual screening tests in infected mice would be needed to detect useful activity" (including drugs that "freeze" antigenic variation; also that promote granulocyte activity); I. B. R. Bowman (discussion) records that in chronic infections rabbit blood pyruvate may reach 60 mg/l. *Pathogenic mechanisms in Chagas' cardiomyopathy* (A. Anselmi, F. Moleiro). *Pathogenesis of Chagas' disease* (F. Koberle).—Emphasis on ganglionic damage, chronicity, and autopsy evidence that Chagas' disease in many areas accounts for ⅓ of adult deaths. *Cutaneous leishmaniasis. The clinical and immunopathological spectrum* (J. Convit, M. E. Pinardi).—Variations in human hosts; photographs of diverse pathologies, some horrendous. *Ultrastructure of pathogenic flagellates* (K. Vickerman). *Immunity and antigenic variation: clinical observations suggestive of immune phenomena in African trypanosomiasis* (P. de Raadt): ". . . little hope . . . for a vaccination technique without . . . antigenic variation being elucidated . . . cultivation of bloodstream forms *in vitro* would mean a considerable step forward." *Nutrition and biosynthetic capabilities of flagellates: problems* in vitro *cultivation and differentiation* (W. Trager).—Post-papers discussion has details on GAM Cross's semi-defined medium for *T. brucei*; infective forms are produced rather unpredictably. *Intermediary metabolism of pathogenic flagellates* (I. B. R. Bowman).—Discussion describes tetrazolium artifacts in locating dehydrogenases; points on behavior of cultured trypanosomatids. *The chemotherapy of trypanosomiasis and leishmanias: towards a more rational approach* (B. A. Newton).—"The need for new trypanocides and leishmanicides cannot be overemphasized"; mapping of some fog-bound terrain; review of the few available drugs; the afterwards discussion broaches the need for trials of drug combinations and presents some Chilean cures by nifurtimox of Chagas' disease. *Drug resistance in trypanosomiasis and leishmaniasis* (W. Peters).—Drug resistance in African trypanosomiasis; again alarm at scarcity of drugs against Trypanosomatidae, due, especially in *leishmania*, to parasite-host intimacy; discussion: Bray notes cures of oriental sore by berberine despite *in vitro* inactivity. *General discussion*: Noteworthy dialogue:

G. A. Mackelt: "It is of tremendous practical importance to have a drug effective against *T. cruzi in vitro* which can be used in blood banks in concentrations which are not toxic for the recipient. We have had to throw more than 21,000 blood samples from antibody carriers (donors) in the last 12 years."

Newton: "Isn't crystal violet satisfactory?"

Mackelt: "Venezuelan people don't like blue blood!"

This book is the stuff to feed the protozoological troops. These able workers grappled in shirt-sleeves, so to speak, with those scourges; no complacencies, many confessions of the kinds of ignorance most deeply troubling. Biologists who think *urgent* is a dirty word in a scientific paper should read the book.

Darkos, G. K. et al., eds. 1974. *Progress in Chemotherapy. Proceedings of the 8th Congress of Chemotherapy. Athens, 1973.* Hellenic Society for Chemotherapy, Athens; distributed in the U.S.A. by the American Society for Microbiology, Washington, D.C. Vol. I, 1022 pp.; sold only with vols. II, 1046 pp. and III, 1022 pp. $68. Vol. I has 9 papers on protozoa: 5 of them on tinidazole (a congener of metronidazole). Subject and author indices.

Five papers on giardiasis; one on a nitroimidazole for amebiasis, giardiasis, and trichomoniasis; from Hoechst (W. Germany) on 250 compounds presenting combinations of mono- or dinitro-

substituted phenyl derivatives, some with aziridine side-chains; tested on hamster model for amebiasis. Novel fused *N*-heterocyclic nitro compounds are proposed for the aforementioned infections, with silence on propensity of nitro aromatics to be toxic, carcinogenic, or both.

N. Ercoli et al. (Venezuela).—Activities of Sb chelates against *Trypanosoma venezuelense* (*evansi*) and *Schistosoma mansoni* in mice do not explain clinical efficacy. F. E. Hahn.—Between discovery of a first lead in chemotherapy research and introduction of a new drug can be as long as 8 years and, as with antibiotics, is beset with the rediscovery problem.

Marois, M., ed. 1975. *Development of Chemotherapeutic Agents for Parasitic Diseases.* Proceedings of an International Conference at Versailles. 1974. North Holland Publishing Co., Amsterdam; American Elsevier, NY. 264 pp.; no indices. $28.30.

M. Sankale et al. (Senegal).—Some foci of sleeping sickness in their country have an "irritante tenacité"; such persistence and recrudescences in Senegal and elsewhere inhibit euphoria about control. They inveigh against the costliness and sporadic availability of drugs. P. de Raadt (WHO) succinctly reviews the history of tryparsamide, suramin, pentamidine, melarsoprol, and nitrofurazone. He discusses also shortcomings and side effects of nifurtimox which limit its usefulness even for cases of Chagas' disease from endemic areas where the parasite is susceptible. In the after-paper discussion, noting that suramin and Berenil are for veterinary use only, he emphasizes that it takes much time for industry to extend a drug from veterinary to medical use. A. A. Buck pleads for more field information to guide drug trials, especially incidence of multiple parasitism. E. H. R. Friedheim, the sole developer of the newer, more effective arsenicals, after reviewing filariasis, Chagas' disease, and sleeping sickness, argues for appreciation of the creative element in chemotherapy research and cooperation among university, industry, and government. A. Dann (W. Germany) engagingly reviews the trails to the basic trypanocides. O. D. Standen (Wellcome) quenches optimism about the prospects of chemotherapy research, as brought out in discussing pursuit of the lead and in presenting a flow chart for the tortuous course from lead compounds to marketing, to the profits underpinning new research.

The printed discussions hint that some sessions might have been heated. Wide experience and insights are exposed on ascariasis, onchocerciasis, patents and practical drug delivery, and the role of WHO. Dann sees as the crucial problem: "In government circles there is still the opinion that for the research in chemotherapy government institutions shouldn't be used because . . . industry will cover the whole field and it would be indecent in the university to do applied research that looks like the development of drugs . . . But to work out a reliable testing system is often beyond the aims and beyond the intentions of industry. They usually go over the literature and try to find out those systems that have been worked out in university biological laboratories with other aims and use them for their purposes. Admittedly, at the universities, it is not possible to set up long-standing biological screening because the personnel is not stable enough and because the running experiences are often beyond the ability of the department. Therefore the screening is one of the bottlenecks for chemists at the universities who are working with more or less bizarre substances that might be of potential use as drugs somewhere or that may give a lead for pursuing new substances and new classes of substances that should not be missed in the general picture of new drugs . . . Furthermore it is up to the universities to do more research on the mechanism of action of existing drugs. That is very cumbersome and it is often beyond the scope of the drug industry." [The old problem: one has the cure, but for which disease?]

The problem was reiterated by Standen: "In contrast to the increase in the incidence and prevalence of some of the major parasitic diseases, there is strong evidence of decline in research in these diseases within the pharmaceutical industry. ". . . if it continues, the outcome could be virtually irreversible. In this event there would be no alternative source of drug development in this field. Although universities can contribute to drug development through basic research and training of specialists, they cannot replace the research and development capacities unique to the pharmaceutical industry."

This elegant symposium should be available to anyone deploying substantial resources for field work and research, and concerned with WHO as coordinator.

Williams, D. D., Geddes, A. M., eds. 1976. *Chemotherapy. Vol. 6. Parasites, Fungi, and Viruses.* (Proceedings of the 9th Int. Congr. Chemotherapy, London, 1975). 434 pp.; Plenum Press, New York and London. £22.05.

Dismay pervades some of the few protozoological papers. A. Bryceson (Hospital for Tropical Diseases, London) queries: "What are the problems in tropical medicine?" and answers: "Neglect," and asserts that criteria laid down by WHO, FDA, and the Committee of Safety of Medicine (UK) virtually arrest progress in certain parasitic diseases . . . "what a mercy we had arsenic and antimony before these committees were born, for we still use both . . . We have no new drugs for sleeping sickness since Melarsoprol was introduced full 30 years ago; and the facts are such now that it is not worth the while [of] a pharmaceutical company to develop a drug even if a promising lead were offered. For even if the drug was given to every patient with the disease in Africa, that company would still not cover its development costs."

Alarm is sounded about onchocerciasis. A. P. Hall: only quinine is effective in chloroquine-resistant *falciparum* malaria, with further dosage with pyrimethamine + sulfadoxine; mefloquine—a new quinoline methanol—replacing pyrimethamine, was slow-acting. W. Peters ("the role of university research departments of antiparasitic chemotherapy") urges: (*a*) chemical development from an established chemical lead, (*b*) biological screening; he complains of the difficulty in pursuading pharmaceutical companies to look for activity against trypanosomiasis, leishmaniasis or filariasis in their general screening program. He pleads (as in the recommendations of the Versailles conference) for intensified collaboration among industry, international and government bodies, and academe. Standen, as at the Versailles meeting, points out the decline in new chemical entities marketed in the U.S., arising from pharmaceutical research: from 63 in 1959 to 11 in 1972, along with declining expenditures for R. & D. E. Winkelmann, W. Raether (Hoechst) update their work on nitroimidazoles disclosed in the Athens symposium, noting activity of HOE 088 (pirinidazole) against *Histomonas meleagridis*, and its effect comparable to those with nifurtimox against *T. cruzi*, with perhaps fewer side effects. Other papers describe another metronidazole congener against trichomoniasis; activity of tinidazole against giardiasis—one paper—in workers

at an international airport. Trimethoprim + sulfamethoxazole seems efficacious, likewise chloroquine in short-range treatment of *falciparum* malaria in Tanzania (T. J. Goosen et al.). Cerisola et al. report some success with a nitroimidazole-acetamide in Chagasic children, judged from a 12-month follow-up by xenodiagnosis and immunological tests. A. M. Mandour & A. M. A. Rahman: metronidazole cured mice infected with *T. evansi* from camels. Other authors: a new polyether is claimed to be as good or better than monensin against various *Eimeria* species in chicks. The papers on antimycotics present few compounds but consolidate much ground, continuing a trend of the Athens symposium.

Van den Bossche, H., ed. 1976. *Biochemistry of Parasite and Host-Parasite Relationships.* (Proceedings 2nd Int. Symp. on the Biochemistry of Parasites and Host-Parasite Relationships, Beerse, Belgium, 28 June-1 July, 1976; organized by the Janssen Research Foundation.) North-Holland Publishing Co., Amsterdam, New York, Oxford. XI + 664 pp. Author and subject indices. $51.95.

Of the 69 papers, 44 concern protozoa.

Trichomonads: metabolism (M. Müller); acetate production (D. G. Lindmark); H_2 production (A. Čerkasovová, J. Čerkasov); nitroimidazoles (Müller et al., C. M. Coombs). *Trypanosomatidae*: electron transport (G. C. Hill); nucleotide synthesis (E. Konigk); kinetoplast DNA (P. Borst, A. H. Fairlamb; Steinert et al., B. A. Newton); use of restriction endonucleases (C. Brack et al., L. Simpson et al.); DNA in *Leishmania* as taxonomic tool (M. L. Chance); ethidium-resistant *T. cruzi* (G. Riou); nucleic acid metabolism in blood and intracellular *T. cruzi* (W. E. Gutteridge); antigens in *T. cruzi* treated with ethidium-DNA complexes (A. Trouet et al.); *T. brucei* (Vickerman et al.); hemolytic effects of *T. brucei* (N. H. Chi et al.); surface antigens of *T. brucei* (G. A. M. Cross & J. G. Johnson); increased virulence of trypanosome infections in mice with malaria or piroplasms (F. E. G. Cox); molecular biology of trypanocides (Newton); effect of ellipticine derivatives on *T. cruzi* (J. Benard & G. Riou); effects of a nitrofuran on *T. cruzi* (P. Sims & W. E. Gutteridge); effect of Berenil on a *Leptomonas* and *T. brucei* (D. G. Daldow & G. C. Hill); effect of suramin on glycerol phosphate oxidase in *T. brucei* (I. B. R. Bowman & A. H. Fairlamb); effect of salicylhydroxamic acid on glycerol phosphate oxidase and *T. brucei* infections in rats (F. R. Opperdoes, Borst); search for antileishmanial agents by means of tissue culture models and mouse infections (W. Peters). *Malaria*: protein synthesis in erythrocytic stage (A. A. McColm et al.); prolonged cultivation (W. Trager; P. I. Trigg, P. G. Shakespeare); histidine-rich protein deom *P. lophurae* (A. Kilejian).

Clarke, F. H., ed. 1976. *Annual Report in Medicinal Chemistry.* Vol. 11. Academic Press (for the Division of Medicinal Chemistry of the American Chemical Society), paperback, compound index. ii + 330 pp. Academic Press, New York. $16.50.

Now for the bottom line: summary articles of better uses of old drugs and advents of new ones. The chapter on antiparasitic agents by E. J. Martin (USDA) occupies 8 pages; 49 of the 71 references concern protozoa as compared with, say, antidepressant and antipsychotic agents (10 p.; 84 refs.) and antineoplastic agents (11 p.; 110 refs.). Antiprotozoal agents are covered in 2.6 pages. The paragraphs on malaria list several reviews; refer to antimetabolites of coenzyme Q; use of the squirrel monkey and rodents; diaminoquinazoline folic antagonists and other new heterocycles including 9-phenanthrene methanols. The brief paragraph on antitrypanosomals and antileishmanials (handy terms!) lists 2 novel compounds with activity for *T. cruzi* and *T. rhodesiense*. There are brief descriptions of new antitrichomonals, coccidiostats, and amebicides. Many of the references are to *J. Med. Chem.*, where biological aspects generally receive minimal discussion.

The antimetabolite concept in drug design is much alive in the chapter by E. F. Rogers (Merck & Co., U.S.A.), who thinks that the best targets are peripheral, species-specific enzyme systems. He cautions that (*a*) drugs that interfere with basic biochemistry increase the danger of toxicity and development of resistance; (*b*) "In practice medicinal chemists cannot wait for solid biochemical rationale"—that many of their discoveries are "premature and provide tools for the chemist," the antithiamine coccidiostat amprolium being a case in point. After discussing the path to be trod "before the design of enzyme inhibitors should become an exercise in solid geometry, followed by challenging synthetic chemistry," he endorses G. H. Hitching's dictum: "enlightened empiricism" is still the best philosophy for medicinal chemists.

Other chapters add to the volume's value. Noteworthy here are those on antineoplastic agents, drug metabolism, membrane regulators (including cytocholasin B), and active transport. In all, a worthy addition to the series aside from its documenting the depressed state of antiprotozoal chemotherapy.

Review of Reviews

The literature burgeons: the already elephantine *Biochemical Sections of Chemical Abstracts* and *Biological Abstracts* inexorably grow heavier. Winnowing the literature for leads to new lead compounds is daunting. How, then, do the publications just reviewed meet the unprecedented need for a tidy, accessible literature? Computer searches have a high noise content: it's still mostly do-it-yourself.

The Caracas Symposium.—Yes. Its price is low by present standards. The authors performed great service in setting forth the present impasses in trypanosomatid therapy and prophylaxis. Seldom have transcripts of discussions—so often random vapidities—been so apropos, pithy, and spirited. Few modern works are so elegantly compact, so excellently referenced and indexed. A landmark book.

The Versailles Volume.—This volume, having different authors, addresses itself to root causes of the situation inspiring the Caracas meeting. Little overlap, since emphasis is on patterns of organization for future research; it includes helminthiases; and it has a specific aim: helping frame guidelines for WHO. Friedheim's injunctions (Versailles volume, p. 155), thereupon loom larger:

"Considering the near astronomic odds against discovery of a valid drug, chances of success are bound to increase with the number of adequate research centres and researchers. Informal exchange of information is desirable, but formal centralization, limiting individual efforts, is not . . . . A central screening facility, available to all workers in the field, would unburden researchers of much routine, but screening requires an informed and imaginative mind if it is not to miss the unexpected which may be IT." [Friedheim's capitals]

The Athens 3 Volumes. By this view, the volumes are a dino-

sauric anachronism: much rather raw data, too wide a range of subjects perhaps for most chemotherapists: essentially an archival work for libraries; printed on thick, glossy paper by a photo process which is uniform throughout, so that those volumes approach the genre of coffee-table books. Yet for the browsing chemotherapist it is good value, particularly for those working with bacterial infections, cancer, and opportunistic infections.

The London Congress.—Unlike its 3-tome Athens predecessors, it is in 8 individually smaller volumes, with the parasitology concentrated handily. The technical papers, unless future events contradict, break little new ground. The more lasting value of the proceedings may be in their forceful reiteration of the dismal state of chemotherapy of trypanosomatid infections and filariasis, including onchocerciasis.

The Belgian Conference.—This volume exemplifies a genre which one may classify as the pretested, sanitized production. It was not open to all, unlike the Athens and London congresses, where the limitations on attendance were the obvious ones of time, money, and the intensity of the hope of receiving or imparting ideas or acquiring collaborators. It differs from the Caracas-Ciba volume, whose low price made it reasonably accessible—an accessibility helped by its being one in a long-established series of moderately priced excellent symposia. The Belgian symposium volume is the 2nd in its series, and expensive even by today's standards despite reliance on camera-ready copy and foundation sponsorship. Its articles do not only review research areas; most of them contain new data. The basic findings and ideas have nearly all previously appeared in standard journals or, as subsequent events show, some of the new data are already being substantiated by journal papers. The residuum of archival papers thus becomes excruciatingly expensive. Nonetheless, the deeply disturbing fault is not one of commission but of omission. In contrast, decades ago, at Cold Spring Harbor, the scheduled program became a shambles because of the irruption and, indeed, practical takeover by the young Monod, Spiegelman, and Lederberg, fire in their bellies, scantily patient with worn orthodoxies. Something of that spirit comes through, as implied, in the discussion reported in the Caracas and Versailles volumes, not in the Belgian one. Perhaps one expects too much. It is outside the scope of this review to hazard why this genre has gained prominence in many fields despite reservations expressed by many reviewers and wails from librarians; analysis of causation may be left to connoisseurs of the Matthew effect, i.e. to those interested in the science of science, notably R. K. Merton and his school in the U.S. and John Ziman in the U.K. One feature of that genre does stand out: in presenting original data by invitation so to speak, it might require rare courage on the part of the reviewing panel, who generally include many of the organizers, to reject data or even whole papers under the twin pressures of conference deadlines and rapid publication. The risks and occasional tortuosities of standard journals' peer-review are lessened; beachheads of priority are more nearly assurable.

Conceivably, the criteria by which the foregoing publications are judged are skewed—that emphasis on the need for new ideas is not *that* justifiable. Two papers received during preparation of this review argue that these criteria and priorities aren't too far off the mark:

(A) The flow diagram for drug development from a lead compound, as presented by Standen in the London and Versailles publications, closely parallels that evolved for showing how the National Cancer Institute (NIH) develops anticancer drugs from microbial and higher-plant sources (Douros, J. D. 1977. *Cancer Treat. Rep.* **60**, 1069-80).

(B) The crucial importance of the lead compound has been emphasized by 2 physical organic chemists with experience with screening for antimalarials: (Hansch, C., Fukunga, J. 1977. Designing biologically active materials. *Chem. Tech.* **7**, 120-8); quotation:

"From the chemist's point of view there are two major problems in drug research. The vastly more difficult one is uncovering new lead compounds of novel structure. Once such a lead is found, the simpler (but by no means trivial) problem is finding the most effective drug suggested by the new lead."

Runaway library costs have seriously cut into available lab-research funds and may curtail grant-financed library expenditures. Therefore recommendations are here offered so as to get the most mileage per hard, austerity dollar:

Get the Caracas volume into the hands of students, if only for them to grasp why landing a voyager on the moon is less dangerous than landing in parts of Africa, South America, and Asia, assuming no re-entry problem. The astronaut returns reasonably intact; the earth-traveller has a good chance of returning with living souvenirs in bloodstream and gut. (Chemistry majors assimilating the astounding advances in organic reaction mechanisms are fair game for the book.) Buy the *Adv. Med. Chem.* paperback for browsing among the bizarre compounds aimed at the vast array of ailments, real to nearly imaginary, that mammal-kind is heir to. Subscribe to the new (1977) *Protozoological Abstracts* (noticed elsewhere in the *J. Protozool.*) so that, with its exhaustive coverage of parasitic protozoa (free-living protozoa are excluded), notice can be taken of the occasional local symposia, many of very limited distribution, issued from Dakar and Nairobi, Coxambu, and Buenos Aires, etc., often cheaply published, and of papers in journals from endemic areas having limited distributions. Some such papers, being predominantly medical, might be listed in the *Clinical* rather than *Life Sciences* edition of *Current Contents.* Acquire, for the crisply authoritative summing up of the present, Goodman, L. S. & Gilman, A., eds., *The Pharmacological Basis of Therapeutics*, 5th (1975) edition (Macmillan); chapters on chemotherapy now by I. M. Rollo. At $30—wonderful value—as a lab-bench companion to the Caracas volume—it compensates for the usual once-over-lightly treatment of chemotherapy still prevalent in textbooks of parasitology. One may thus acquire, despite few absences from the lab, a sense of goings-on in the field. Who dares predict whence Friedheim's "IT"—the updated Ehrlichian magic bullets—will come? Some (as now) may be metallic, or of weird organic design, or antigenic. Here, then, are one person's choices in balancing lab-bench research dollars against symposium or Congress publication dollars.